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Review Article

A Review on Microspheres and Its Role in Different Drug Delivery System as a Novel Approach

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ABSTRACT

Microspheres, which range in size from 1 to 1000 µm, are synthetic polymers or proteins that display the characteristic of freely flowing granules. A wide range of microsphere preparation methods can be employed to control different elements of the material and increase the therapeutic efficacy of a certain medicine while it is being administered. There are several approaches of achieving prolonged controlled release of a substance at the intended place. Microspheres are helpful for many different applications, including medication administration, spacer applications, and medical diagnostics. Microspheres provide less dosage requirements, a longer duration of therapeutic efficacy, consistent medication absorption, and minimal side effects. They also offer effective encapsulation, are adaptable, and reasonably priced. This overview aims to provide a current summary of the most recent developments in innovative drug delivery techniques using dosage forms in the form of microspheres.

INTRODUCTION

Microspheres are one type of polymer-based medicine delivery device. The Greek term "meros," which refers to large molecules connected by covalent bonds in repeating configurations, is where the word "polymer" originates. Spherical particles, also called microspheres, have a size range of high nanometer to micron. Microspheres are materials that are flexible and have special qualities that make them useful in a variety of applications. The synthesis process of the material allows for the customization and control of its size, form, and content. The most effective method for manufacturing microspheres will depend on the type of polymer that best matches the desired

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microsphere properties and the particular application. Microsphere systems are frequently used to modify drug delivery systems. [1] Medication formulations' bioavailability can be improved by using the microsphere system. A substantial improvement in the drug's bioavailability can be achieved by manufacturing asenapine maleate (ASM) microspheres utilizing poly (lactic acid-co-glycolic) as an agent for schizophrenia therapy [2]. The bioavailability of salbutamol sulfate microspheres made with cross-linked chitosan and carrageenan can be improved 1.61 times over that of salbutamol tablets sold in stores. Comparably, research conducted in vitro on cell lines derived from hepatocellular carcinoma have shown that doxorubicin's fatal effect can be enhanced by its biodegradable alginate microsphere formulation with a high concentration of NaHCO3. The microsphere system can be used to disguise the taste of medications in addition to being a vehicle for their delivery. The manufacturing process is discovered to drastically affect the release profile and flavor masking impact of ibuprofen microspheres, which are manufactured with octa decanol and glycerine mono stearate as components. [3].

Microspheres are small spherical particles with a diameter typically between 1 and 1000 µm. As seen in picture 1, microspheres are also referred to as microscopic particles. The microspheres were created using a variety of polymers and then assessed for various uses. There is a wealth of research on the application of microspheres in drug delivery. With little negative effects, the dosage can progressively be decreased because a steady plasma concentration is maintained. [4]

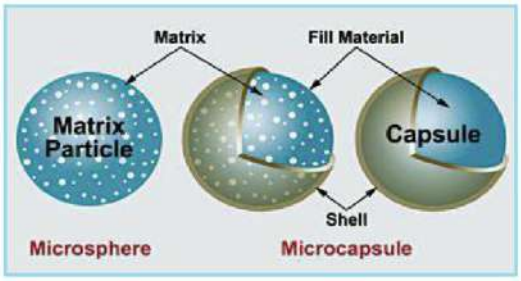

Figure1: microspheres

Advantages of Microspheres

1. Decreased size of microsphere contributes increased surface area thereby increases the potency of the poorly soluble material.
2. Dose frequency and adverse effects can be reduced.
3. Increased patient compliance.
4. Drug packaged with polymer prevent drug from enzymatic cleavage therefore the drug can be protected from various enzymes.
5. Enhances bioavailability.
6. Gastric irritation can be reduced.
7. Biological half-life can be enhanced.
8. First pass metabolism can be reduced.
9. Unpleasant odour and taste of the drug can be masked. [5]

Disadvantages of microspheres

1. Reproducibility is less.
2. The cost of materials and processing is high compared to conventional preparations.
3. Change in process variables such as change in temperature, pH, solvent addition and evaporation/agitation may influence the stability of core particles.
4. The fate of polymer matrix and additives. [6]

Materials used in the formulation of microsphere

Microspheres are usually made of polymers, they are classified as follows.

• Synthetic Polymers
• Natural polymers

A. Synthetic polymers are of two types

a) Non-biodegradable polymers

Eg- Acrolein, Polymethylmethacrylate (PMMA), Epoxy polymers, Glycidyl methacrylate

b) Biodegradable polymers

Eg- Glycolides and their co polymers, Poly alkyl cyano acrylates, Poly anhydrides and lactides.

B. Natural polymers – These are obtained from different sources such as proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Collagen and gelatin

Carbohydrates: Agarose, Carrageenan, Starch, chitosan, Chemically modified carbohydrates: Poly dextran, Poly starch. [7,8]

TYPES OF MICROSPHERES

Microspheres are classified into different types. They are of following types:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres

I. Biodegradable polymeric microspheres

II. Synthetic polymeric microspheres. [9,10]

TECHNIQUES FOR MICROSPHERE PREPARATION

1. Solvent evaporation
2. Single emulsion technique
3. Double emulsion technique
4. Phase separation coacervation technique
5. Spray drying and spray congealing
6. Solvent extraction
7. Quassi-emulsion solvent diffusion [11,12]

Gastro-retentive microspheres drug delivery

A gastro-retentive system, depicted in figure 2, is a kind of delivery system intended to prolong the half-life of medicinal chemicals in the stomach. Several polymer types have been used to modify the system in order to produce microspheres that can endure longer in the digestive system. Alogliptin, simvastatin, furosemide, pregabalin, gabapentin, and other systemic drugs were designed to be administered using gastro-retentive delivery devices that employed microsphere formulations. Generally speaking, the goal of these microspheres is to increase bioavailability by prolonging the time that a medicine is present in the stomach. [13–15]. The significant variations in polymer choice also influence the process used to create the microspheres. Polymers that are able to expand and float in stomach fluids are typically selected for the gastro-retentive system. The emulsion solvent evaporation method is the most widely used in formulation due to its ease of manufacturing. This method creates microspheres by spreading an emulsion of the polymer solution in an organic solvent and then letting it evaporate. [16–18]. Several diffusion-regulated microsphere formulations for in vitro drug release followed the kinetics described by Higuchi and Korsmeyer Peppas. In its non-fiction form, the in vitro drug release mechanism was regulated by the expansion and contraction of the polymer. Microspheres can boost oral bioavailability and release medications in a regulated manner, lowering the frequency of administration and enhancing patient compliance by fusing the benefits of floating and muco-adhesiveness. [19] Summary of gastro-retentive microspheres is given in table 1.

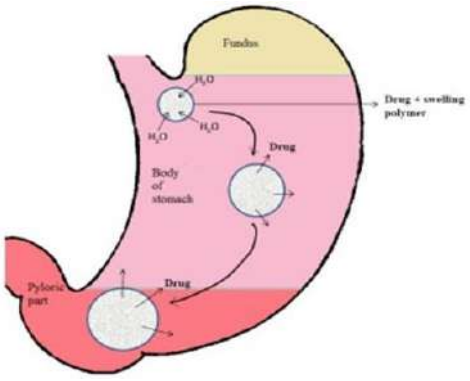

Figure 2: Gastro-retentive microspheres drug delivery

Table1: Summary of gastro-retentive microspheres drug delivery [20-26]

Sr.No.	Active substance	Polymer	Method
1	Amoxicillin trihydrate	Sterculiafoetida-pullulan-based semi-interpenetrating polymer	Emulsion cross-linking

2	Alogliptin	Cellulose acetate butyrate (CAB) and polyethylene oxide (PEO)	Emulsion solvent evaporation
3	Bletillastriata polysaccharide	Sodium Alginate	Ionotropic gelation
4	Famotidine	Locust bean gum (LBG) and polyvinyl alcohol (PVA)	Emulsion cross-linking
5	Simvastatin	HPMC K4M as carrier polymer and Eudragit RSPO	Spray drying
6	Famotidine (FX) and clarithromycin (CLX)	Thiolatedpolyacrylic acid (TPA)	Emulsion solvent evaporation
7	Nifedipine	Poloxamer 407 and carbopol 934	Single emulsion cross-linking
8	Lafutidine	Chitosan	Emulsion solvent evaporation
9	Furosemide	Ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC)	Emulsion solvent volatilization
10	Itraconazole	Ethyl cellulose as a low-density polymer and Eudragit E100 as a release modifier	Emulsion solvent diffusion-evaporation
11	Pregabalin	Ethyl cellulose (EC) and polyvinyl pyrrolidone (PVP)	W/O/O multiple emulsion
12	Lafutidine	Eudragit Grades	Emulsion Solvent Evaporation
13	Pregabalin	Pectin	Ionotropic Gelation
14	Famotidine	Mimosa pudica seed mucilage as a natural mucoadhesive polymer	Ionic gelation
15	Gabapentin	HPMC K100	Solvent evaporation

Colon microspheres drug delivery

Using the microsphere technology to concentrate drugs for the colon is standard procedure. The kind of polymer chosen is an important consideration. The polymers selected must be able to withstand passage through the upper gastrointestinal tract in order to guarantee that the drug reaches the colon. Generally speaking, this method was created for drugs that have limitations while in the gastrointestinal tract or that have confined effects in the colon. This technique is used to administer a number of non-steroidal anti-inflammatory medications, which are used to treat ulcerative colitis. The purpose of ileocolonic flurbiprofen muco adhesive microspheres is to prevent stomach side effects while improving patient compliance. Core microspheres were made by emulsifying and cross linking chitosan, which is used as a polymer. Subsequently, an emulsion solvent evaporation method was employed to coat them with enteric coating polymers, specifically Eudragit L100 and Eudragit S100, in order to establish a delivery system tailored to the colon. [27]

For colonic administration, different medication formulations opt to use pH-sensitive polymers of the Eudragit class [28]. The USP dissolving device II was used to evaluate the in vitro drug release from the microspheres in pH 7.4 phosphate buffer. [29,30].

These two natural polymers, sodium alginate and fenugreek seed mucilage, can be delivered via the colon by using the ionic gelation method to convert them into microspheres. Because this polymer can tolerate the conditions encountered in gastric fluid, it can be utilized to give 5-fluorouracil for the treatment of colon cancer. [31,32] Colic delivery preparations also use polymers, such as alginate, that are sensitive to pH. The preparation strategy that is employed will surely depend on the kind of polymer that is chosen. For ionically charged polymers, for instance, researchers usually use ionic gelation

techniques to establish strong cross-linked linkages between polymers. Figure 3 depicts the colon microspheres' drug delivery, and Table 2 provides a description of the colon microspheres' drug delivery. [33, 34]

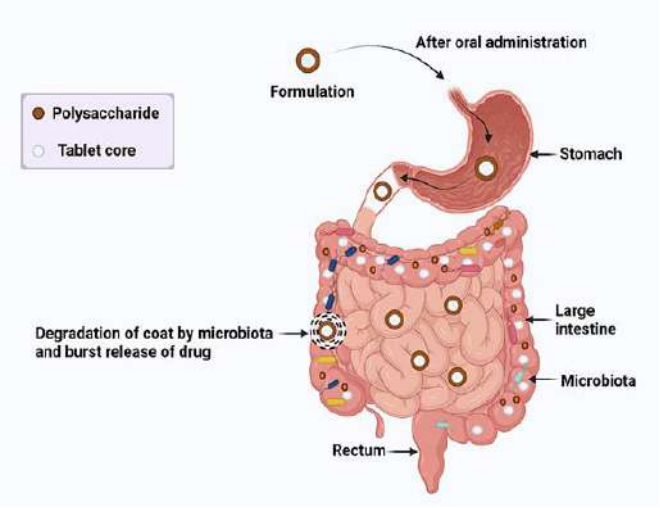

Figure 3: Colon microspheres drug delivery

Table 2: Summary of colon microspheres drug delivery [35-40]

Sr. No.	Active substance	Polymer	Method
1	Epigallo catechin gallate	Chitosan (CS) and Gum acacia (GA)	Water-in-oil emulsion crosslinking
2	Mesalamine	Sodium alginate and pectin	Ionic gelation
3	Progesterone	Pectin and Na CMC	Ionic gelation
4	Meloxicam	Sodium alginate and Eudragit-coating	Ionotropic gelation
5	Piroxicam	Pectin and Zein	Ionic Gelation
6	Ibuprofen	Thiolated jackfruit seed starch	Ionic gelation
7	Puerarin	Alginate	Emulsification/internal gelation
8	Dicyclomine hydrochloride chitosan	Ethylcellulose as a low-density polymer and Eudragit E100 as a release modifier	Emulsion crosslinking and solvent evaporation
9	Lactobacillus rhamnosus GG, LGG	Eudragit® S100	Spray drying
10	Fluorouracil and Oxaliplatin	Alginate and guar gum polymers for Fluorouracil. Alginate and chitosan polymers for Oxaliplatin. Coated with Eudralgit s100	Ionotropic gelation
11	5-fluorouracil	fenugreek seed mucilage-sodium alginate	Ionotropic gelation

Nasal and pulmonary microspheres drug delivery system

In cases of respiratory tract irritation, systems for delivering drugs through the nose and lungs are starting to appear as an alternative to oral medication administration. These devices are usually used for the administration of small-dose drugs. Nasal and pulmonary microspheres take advantage of the natural mucosa of the respiratory system. Medication that is breathed and exhaled can have its bioavailability increased by the application of muco-adhesive polymers. [41]

Chitosan is one of the polymers that is most frequently used in pulmonary and nasal delivery systems. The presence of an amine group in the material determines a number of chitosan's properties, such as its cationic qualities, ability to control drug release, mucoadhesive qualities, in situ gelation, antibacterial qualities, permeability enhancement, and so on. Extending the duration of drug residence in the nasal cavity through the use of chitosan microspheres in nasal and pulmonary preparations has been demonstrated to augment the local and systemic effects of medication therapy. Potential mucoadhesive polymers include alginate, gellan gum, polylactic-co-glycolic acid, pectin, and hypromellose. [42].

Ciprofloxacin HCl microspheres based on carrageenan polymers have been reported to be offered as a dry powder inhalation dosage form. The microspheres were successfully produced using the ionic gelation technique, and it has been shown that these improved drug release mechanisms and bioavailability in the pulmonary system. The medication delivery method for nasal and pulmonary microspheres is summarized in Figure 4 and is associated with the drugs indicated in Table 3. [43]

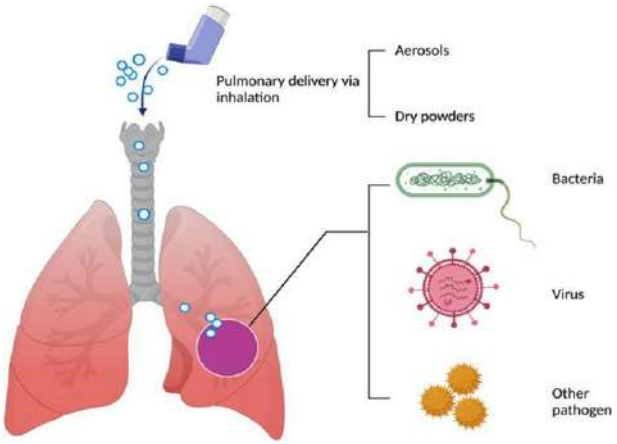

Figure 4: Nasal and pulmonary microspheres drug delivery system

Table 3: Summary of nasal and pulmonary microspheres drug delivery [44-51]

Sr. No.	Active substance	Polymer	Method
1	Astragalus polysaccharide	Chitosan	Spray-Drying
2	Ciprofloxacin HCl	Carrageenan	Ionic Gelation
3	Donepezil Hydrochloride	Gellan gum	Spray-Drying
4	Granisetron	Chitosan	Emulsification cross-linking
5	LurasidoneHCl	Chitosan and Eudragit L 100	Spray-Drying
6	Melatonin	Pectin and Hypromellose	Spray-Drying
7	Mometasonefuroate	Poly (lactic-co-glycolic acid)	Solvent evaporation
8	Ropinirole hydrochloride	Alginate	Spray-Drying
9	Tetanus toxoid	Trimethyl chitosan	Ionic gelation

10	Sildenafil Citrate	Sodium Carboxymethyl Cellulose, Sodium Alginate, And Sodium Hyaluronate	Spray-Drying

Parenteral microspheres drug delivery system

Microspheres as a depot mechanism enable controlled medication administration for parenteral formulations. The creation of glatiramer acetate (GA) microspheres, which were initially meant to prevent the recurrence of multiple sclerosis, is one such instance. This medicine is usually delivered by repeated subcutaneous injections, once a day or twice a week, due to how quickly it departs the body. In order to prevent the patient from needing to get repeated injections, a poly (lactic-co-glycolic acid) polymer implant was created as a parenteral microsphere system to administer the drug continuously and gradually. [52,53] Poly (lactic-co-glycolic acid) is the most widely used polymer in microsphere compositions intended for parenteral administration. Parenteral microsphere preparations are frequently injected subcutaneously and intramuscularly, with the tissues—muscle, for instance—acting as a mechanism of releasing adipose tissue and storing energy. [54] Figure 5 depicts the parenteral microspheres drug delivery system, and Table 4 lists the medications that can be administered via this method.

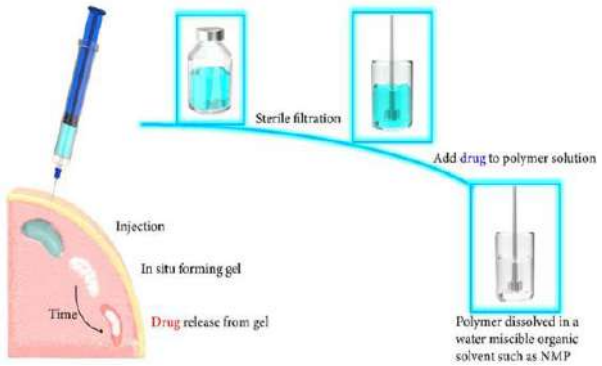

Figure 5: Parenteral microspheres drug delivery system

Table 4: Summary of Parenteral microspheres drug delivery [55-59]

Sr. No.	Active substance	Polymer	Method
1	Aripiprazole	Polycaprolactone	O/W Emulsion Solvent-Evaporation
2	Bovine serum albumin (BSA)	Poly (lactic-co-glycolic acid)	Double emulsion solvent evaporation
3	Curcumin	Alginate	Emulsification/gelation
4	Flurbiprofen, Lidocaine, or Risperidone	Various grades of poly (lactic-co-glycolic acid) or Ethylcellulose	Solvent Evaporation
5	GnRH agonist leuprolide acetate	Poly (lactic-co-glycolic acid)	Double emulsion solvent evaporation
6	Glatiramer acetate	Poly (lactic-co-glycolic acid)	Emulsification
7	Ivermectin	Polycaprolactone	Solvent Evaporation
8	Leuprolide Acetate	Poly (lactic-co-glycolic acid)	Solvent evaporation

9	Leuprolide Acetate	Poly (lactic-co-glycolic acid)	Solvent evaporation
10	Celecoxib, Clotrimazole, Erythromycin, Ibuprofen, Indomethacin, Itraconazole, Lopinavir and Ritonavir	Poly (lactic-co-glycolic acid)	Solvent Evaporation
11	Paliperidonepalmitate	Poly (lactic-co-glycolic acid)	Oil in water (O/W) emulsion solvent evaporation
12	Human Chorionic Gonadotropin (hCG) hormone	Poly (lactic-co-glycolic acid)	A modified double emulsion solvent evaporation
13	Regorafenib	Poly (lactic-co-glycolic acid)	Emulsion-Solvent Evaporation

Ocular microspheres drug delivery system

The primary goal of incorporating microspheres into ocular preparations is to address an issue with traditional aqueous eye drop formulations, specifically the medication's quick evacuation from the eye. The microspheres' persistent attachment to the ocular surface increases the bioavailability of the encapsulated medication. A range of methods, such as erodible microparticulates, swelling muco-adhesive particulates, pH-responsive microparticulates, nanoparticles and latex systems, and ion-exchange resins, can be used to synthesize medications in micro-particulate dosage form for intraocular and topical distribution. [60]

Polymers have been used to create injectable particles and ocular implants. One of the most popular biodegradable polymers in ocular controlled drug delivery systems is poly (lactic-co-glycolic acid). In an aqueous environment, like the eye, poly (lactic-co-glycolic acid) water-soluble byproducts progressively break down and alter. Chitosan microspheres loaded with levofloxacin offer prolonged drug release that can be used to treat eye infections. [61] Timolol maleate can be administered regularly to treat glaucoma with semi-interpenetrating polymer microspheres as an ocular delivery device. [62] Figure 6 depicts the ocular microspheres drug delivery system, and Table 5 lists a review of the medicines that are available for use in this system.

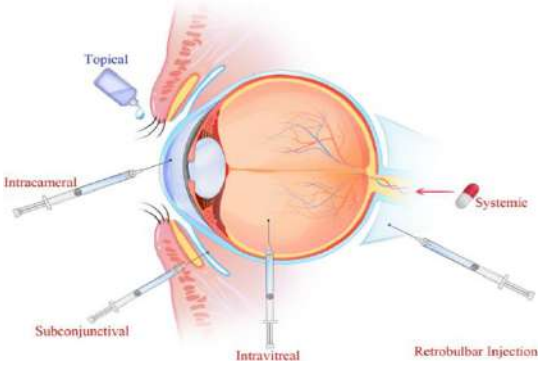

Figure 6: Ocular microspheres drug delivery system

Table 5: Summary of ocular microspheres drug delivery [60-62]

Sr. No.	Active substance	Polymer	Method

1	Atorvastatin Calcium-Poly-E-Caprolactone	Methylcellulose (MC) and Polyvinyl Alcohol (PVA)	Solvent evaporation
2	Dexamethasone	Poly(lactic-co-glycolic acid)	Oil-in-water (O/W) emulsion solvent evaporation technique
3	Dexamethasone and fibronectin	Poly(lactic-co-glycolic acid)	Water-in-oil-in-water emulsion method including dexamethasone in the organic phase and fibronectin in the inner aqueous phase
4	Dexamethasone (DX), Melatonin (MEL) And Coenzyme Q10 (Coq10)	Poly(lactic-co-glycolic acid)	Oil/Water emulsion solvent extraction-evaporation
5	Bevacizumab	Poly(d, l-lactide-co-glycolide)/poly (cyclohexane-1,4- diyl acetone dimethyleneketal)	Solid-In-Oil-In-Water (S/O/W) Emulsification
6	Levofloxacin	Chitosan	Spray-drying technique
7	Sunitinib malate	Poly(lactic-co-glycolic acid)	Emulsification method.
8	Timolol Maleate	Psyllium (PSY) and polyvinyl alcohol (PVA)	Emulsion cross-linking method
9	Glial cell-line-derived neurotrophic factor-GDNF and Tauroursodeoxycholic acid-TUDCA	Poly(lactic-co-glycolic acid)	Solid-in-oil-in-water (S/O/W) emulsion solvent extraction-evaporation technique

Topical microspheres drug delivery system

Medication can be delivered to particular target locations on the skin using microspheres as carriers. Medication can be contained in microspheres to offer a controlled release and extended pharmacological impact. Drugs can be continuously delivered using microspheres for a prolonged duration. The efficacy of therapy can be enhanced and therapeutic medication levels preserved in the skin through the controlled release of pharmaceuticals from microspheres. Through improved drug penetration into the skin and increased drug bioavailability, microspheres may improve topical therapy's therapeutic efficacy. [63] A sunscreen cream that uses Benzophenone-3 microspheres aims to continuously release the sunscreen chemical through the cream's microspheres. Sunscreen cream applies smoothly, has a milky white color, and has a uniform consistency. It also spreads and extrudes readily. [64] Topical microspheres drug delivery system shown in figure 7 and list of drugs that are available in topical microspheres listed in table 6.

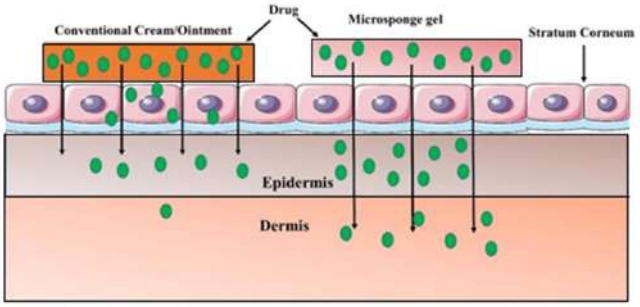

Figure 7: Topical microspheres drug delivery system

Table 6: Summary of topical microspheres drug delivery [64,65]

Sr. No.	Active substance	Polymer	Method
1	Acyclovir	Polyvinyl Alcohol (PVA)	Quasi-emulsion diffusion
2	Benzophenone-3	Gelatin	Emulsion cum thermal gelation technique
3	Clarithromycin	Ethylcellulose	Quasi-emulsion solvent diffusion
4	Glutathione	Alginate	Ionotropic gelation method by aerosolization
5	Graphene–ketoconazole nanohybrid (Gn-keto)	Polymethacrylate derivative Eudragit	Spray-drying technique
6	Metronidazole	Chitosan and alginate	Ionotropic-gelation technique,
7	Nisin	Sodium alginate-gelatin	Ionotropic gelation
8	Usnic Acid	Eudragit	Solvent evaporation

Characterization/ Evaluation of Microspheres

1. **Particle size and shape:** By using calibrated optical micrometer, light microscopy (LM) and Scanning electron microscopy (SEM)
2. **Electron spectroscopy for chemical analysis:** The electron spectroscopy for chemical analysis (ESCA) is used to determine the surface chemistry of the microspheres.
3. **Attenuated total reflectance Fourier Transform Infrared Spectroscopy:** FT-IR is used for the determination of degradation of the polymeric matrix of the carrier system. The microspheres' surface is examined by measuring alternating total reflectance (ATR).
4. **Density determination:** The density of the microspheres is measured by using multi volume pycnometer.
5. **Isoelectric point:** Electrophoretic mobility of microspheres can be measured using micro electrophoresis from which the isoelectric point is determined.
6. **Determination of percentage yield:** The percentage yield is determined by calculating the measured amount of the product and the polymers used in the formulation of the microspheres and the overall sum of microspheres produced.
7. **Determination of drug loading:** Drug loading is the amount of drug loaded per unit nanoparticle weight, indicating the percentage of nanoparticle weight which is attached to the encapsulated product. Drug loading (%) can be determined by the total amount of drug entrapped, divided by the total weight of nanoparticles. [66,67]

Pharmaceutical Application Of Microspheres

I. Microspheres in vaccine delivery
II. Microspheres in Gene delivery
III. Oral drug delivery
IV. Transdermal drug delivery
V. Targeting by Using Micro Particulate Carriers
VI. Monoclonal Antibodies [68-70]

CONCLUSION

Microspheres can be used in a variety of medication delivery methods, including topical,

parenteral, nasal and pulmonary, intestinal, and ocular. The delivery method that will be used ultimately dictates the kind of polymer that is used. The preparation procedure for microspheres is largely influenced by the characteristics of the polymer type and the active ingredient. In the last few years, the majority of microsphere research has focused on their application in nasal and pulmonary delivery systems; topical delivery methods have gotten the least amount of attention. Future studies can evaluate the characteristics of the microspheres in each drug delivery technique.

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